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09/714,449	11/16/2000	Gabriel Vogeli	00237.US1	5102

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EXAMINER

MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	21

DATE MAILED: 12/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,449	VOGELI ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 05 June 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,3,5,8-28,31-35 and 98 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1,3,5,8-28,31-35 and 98 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 18.

4) Interview Summary (PTO-413) Paper No(s). _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

Formal Matters

Claims 1, 3, 5, 10, 13, 27-28 were amended, and new claim 98 was added, in Paper No. 20, 6/5/2003. Claims 1, 3, 5, 8-28, 31-35, 98 are pending and under consideration.

Response to Amendment

Applicant's arguments filed 6/5/2003 have been fully considered, but they are not persuasive in part.

The objection to claims 1, 3, 5, 11-13, 27-28 has been obviated by Applicant's amendment and is thus withdrawn.

The rejections of the cancelled claims have been rendered moot, and are thus withdrawn.

New and remaining issues are set forth below.

Claim Objections

Claims 33-35 are objected to because of the following informalities: They contain limitations drawn to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 stand rejected, and new claim 98 is rejected, under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby, for reasons of record set forth in Paper No. 17, 12/2/2002. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The rejection of record set forth that it is clear from the instant specification that the nucleic acid encoding the NGPCR-54 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 18, line 11). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al. 1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork

et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, even if, *arguendo*, the nucleic acid encoding the NGPCR-54 protein is found to be a G-protein coupled receptor, it is an orphan receptor. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the NGPCR-54 protein, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. In the instant case, the fact that the claimed invention encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific ligand for each receptor is known, unless the biological activity of the receptor is disclosed and unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in

the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as NGPCR-54, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is known to be structurally analogous to proteins that are known in the art as G protein coupled receptors. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit its activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for NGPCR-54 then the claimed

invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 1-35 stand rejected, and new claim 98 is rejected, under 35 U.S.C. 112, first paragraph, for reasons of record set forth in Paper No. 17, 12/2/2002. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues that the claimed polynucleotide encodes a G protein coupled receptor and that the class of proteins which are G protein coupled receptors (GPCRs) have a well-established utility. Applicant cites Marchese et al. which sets forth that the identification of GPCR's is a task of prime importance. However, the Marchese reference also teaches that when homology is less than 35% ligand identification is challenging. As the rejection set forth, in the absence of knowledge of the natural ligand or biological significance of this protein, there is no immediately obvious patentable use for it. Applicant further argues that the polynucleotide encoding nGPCR-54 has a utility because it could be used to screen for a ligand to nGPCR-54. First, this is an admission that the ligand to nGPCR-54 is indeed unknown. Secondly, orphan G protein-coupled receptors do not have a well-established use, in that all GPCRs do not function exactly alike. Each GPCR is unique in the ligand that binds it, which determines what signal to be transmitted and thus what biological effect to be conveyed by said receptor. In the instant case, the fact that the claimed invention encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific

ligand for each receptor is known, unless the biological activity of the receptor is disclosed and unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility.

Applicant further argues that the Office has granted other applications directed to GPCRs, and thus is precluded from making a utility rejection in this application. However, each application stands or falls on its own merits, and the Office is not estopped from making any rejection over a pending application that is consistent with 35 USC § 101. Applicant additionally argues that it was well known in the art at the time of filing that nucleic acids were useful for toxicology testing in microarrays, and cites Nuwaysir et al. and Rockett et al. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case all nucleic acids and genes are in some combination useful in selectivity screening. However, the particulars of selectivity screening with SEQ ID NO: 85 are not disclosed in the instant specification. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of DNA, but is only potential with respect to SEQ ID NO: 85. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for selectivity screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of DNA.

Applicant further argues that the polynucleotide can be used as a tissue specific probe because it is expressed in tissues of particular clinical interest (including brain, kidney, lung, muscle, testis, heart, liver, ovary, prostate, small intestine, spleen and peripheral blood cells; see page 121, lines 25-29 of the specification). However, there must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in eosinophils to the exclusion of normal tissue or is expressed in higher levels in the diseased state compared to normal expression (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide and any disease, disorder or condition and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Applicant additionally argues that the polynucleotide can be used for the used as a chromosomal specific probe. However, This asserted utility is not specific and substantial. Such assays can be performed with any polynucleotide. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

The rejection of record set forth that even if, *arguendo*, the claims are found to have a patentable utility, claims 1-35 stand rejected and new claim 98 is rejected under 35 U.S.C. 112,

first paragraph, because the specification, while being enabling for a nucleic acid encoding an amino acid of SEQ ID NO: 85, or a nucleic acid with the sequence as set forth in SEQ ID NO: 86, does not reasonably provide enablement for a nucleic acid encoding an amino acid which is a fragment of SEQ ID NO: 85 for reasons of record set forth in Paper No. 17, 12/2/2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-35 and 98 are overly broad since insufficient guidance is provided as to which of the myriad of variant nucleic acids encode polypeptides which will retain the characteristics of NGPCR-54. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of NGPCR-54. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Since the claims encompass variant nucleic acids and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The

claims as written do not set forth a functional limitation for the polynucleotides which encode polypeptides encompassed by the claims. Since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant has amended claim 1 to include a limitation whereby the encoded polypeptide comprises an epitope specific to the polypeptide. However, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and polypeptides that the specification only teaches one skilled in the art to test for functional variants. Since the claims do not enable one of skill in the art to make and use the claimed polynucleotides and polypeptides, but only teaches how to screen for the claimed polynucleotides and polypeptides, and since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims.

Claims 1-35 stand rejected and new claim 98 is rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention, for reasons of record set forth in Paper No. 17, 12/2/2002. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims. The claims are drawn to a nucleic acid encoding an amino acid which is a fragment of SEQ ID NO: 85. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded SEQ ID NO: 85. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid with a sequence as set forth in SEQ ID NO: 86, and the polypeptide of SEQ ID NO: 85 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant has amended claim 1 to include a limitation whereby the encoded polypeptide comprises an epitope specific to the polypeptide. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polynucleotides and encoded polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. in the instant case, there is no functional limitation set forth for the encompassed polynucleotide and polypeptide variants. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be since no functional limitation is set forth. Thus, no identifying characteristics or properties of the instant polynucleotide s and polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "said seven transmembrane receptor protein" in line 4. There is insufficient antecedent basis for this limitation in the claim, or in claim 1 from which it depends.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
November 20, 2003


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